Summary Basis for Regulatory Action

Date: December 19, 2012
From: Michael Kennedy, Chair of the Review Committee
BLA/ STN#: STN 125389/0
Applicant Name: Biotest
Date of Submission: November 3, 2010
PDUFA Goal Date: December 26, 2012
Proprietary Name/ Established Name: Bivigam™/ Immune Globulin Intravenous (Human), 10%
Indication: Treatment of Primary Immune Deficiency patients
Recommended Action: Approval
Signatory Authorities Action:
Offices Signatory Authority: for Jay S. Epstein M.D., Director, OBRR,

☐ **I concur with the summary review.**

☐ **I concur with the summary review and include a separate review to add further analysis.**

☐ **I do not concur with the summary review and include a separate review.**

Offices Signatory Authority: Mary Malarkey, Director, OCBQ,

☐ **I concur with the summary review.**

☐ **I concur with the summary review and include a separate review to add further analysis.**

☐ **I do not concur with the summary review and include a separate review.**

Material Reviewed/Consulted and Specific documentation used in developing the SBRA: Reviewer Name
Clinical Review: Mitchell Frost
Clinical Pharmacology Review: Harold Boxenbaum
Statistical Review: Jessica Kim
CMC Review: Michael Kennedy/Malgorzata Norton/Douglas Frazier/Liza Virata/,Lilin Zhong/Pei Zhang
Pharmacology/ Toxicology Review: Evi Struble
Biomonitoring Review: Lillian Ortega
Facilities Review (DMPQ): Rebecca Olin/Peter Amin/Destry Sillivan
Labeling Review (APLB) Alpita Popat
Pharmacovigilance Review: Scott Winiecki
RPM: Pratibha Rana

1. Introduction

This Original Biologics License Application (BLA) submission from Biotest Pharmaceuticals Corporation (BPC) was submitted on November 3, 2010 and is for a new intravenous 10% human immune globulin with the proposed trade name, "Bivigam™" and is indicated for the treatment of Primary Immune Deficiency Disorders. Bivigam is a sterile 10% protein solution formulated in (b)(4) glycine, (b)(4) NaCl, and (b)(4) polysorbate 80 (PS-80) at pH 4.0-4.6, without any sugar stabilizer or albumin. Bivigam is manufactured from US Source Plasma (----------(b)(4)----------) by a modified Cohn-Oncley cold alcohol fractionation process and with two added viral inactivation/removal steps - solvent/detergent treatment (Triton X-100/tri-n-butyl phosphate) and nanofiltration (35 nm filter). The manufacture, in-process testing, and the majority of the final product release testing are performed at the BPC Boca Raton, FL facility. Filling into final container vials is performed under contract at ----------(b)(4)----------. The product is supplied in 50 and 100 mL -(b)(4)- clear ---(b)(4)--- glass vials with gray ----------(b)(4)---------- rubber stoppers and aluminum seals with plastic flip-off caps. "All containers and materials used in bulk drug substance and drug product are latex free." The proposed shelf life of Bivigam is 24 months, stored at 2-8 ºC.

The review of this BLA proceeded smoothly but a regulatory determination was delayed by modifications at BPC's Boca Raton facility and the manufacturing and comparability testing of additional conformance lots. The sponsor planned to perform facility upgrades during the review period for this BLA and these upgrades caused a number of delays. A Complete Response letter was issued on September 1, 2011 because of a delay in manufacturing conformance lots. BPC supplied a complete response on October 26, 2011 to initiate the second review cycle for this BLA. A second CR letter was issued on April 26, 2012 because of issues related to viral clearance studies, cleaning validation, and ----------(b)(4)---------- testing. A third CR was issued on August 6, 2012 because of issues related to ----------(b)(4)---------- testing.

2. Background

Biotest Pharmaceuticals Corporation (BPC) was founded in December 2007 after the purchase of the former Nabi Biopharmaceuticals Plasma Therapeutics manufacturing facility in Boca Raton, FL by Biotest AG of Dreich, Germany. BPC acquired full rights to Nabi-HB® as well as a number of INDs and preclinical assets. One of the assets acquired was an ongoing clinical trial for an IGIV therapy: Investigational New Drug Application 13353, submitted April 13, 2007; Protocol Nabi-7101, "*Open Label, Phase III Safety, Efficacy, and Pharmacokinetic Study of Nabi-IGIV 10% Immune Globulin Intravenous-Human in Subjects with Primary Immune Deficiency Disorders (PIDD*)." Biotest completed the clinical study for the IGIV product on 24 Jul 2009. The BLA 125389/0 contains the data from this single phase 3 trial to determine safety, efficacy, and pharmacokinetics of Bivigam in PIDD patients.

At the time of completion of the clinical trial, BPC approached the Agency regarding changes to the manufacturing facility in Boca Raton, FL. BPC held a Type C meeting with the Agency (CRMTS # 7141) in June 2009 to discuss their planned facility modifications, and informed CBER that it planned to perform the modifications in 2 separate phases. The Agency advised the firm to perform 2 separate runs of 2 conformance lots each for each phase of facility modification. BPC completed the first phase of the improvements to the IgG manufacturing facility in December 2009. This first phase of facility modifications involved significant changes to the facility and manufacturing equipment including: ----------
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In February 2010, BPC manufactured the first 2 conformance lots to be used for comparability studies between the two sets of conformance lots as well as the clinical material. These lots were manufactured at the anticipated commercial scale via the intended commercial process, were placed on stability testing program, and release-tested. The second phase of facility modifications was not completed until March 2011 and completion of equipment validations further delayed manufacture of the second set of conformance lots until September 2011.

3. Chemistry Manufacturing and Controls (CMC)

a) Product Quality

Source Plasma: BPC obtains US source plasma from licensed centers operated by BPC, and from other FDA licensed plasmapheresis centers qualified by BPC. The plasma conforms to the regulations of the FDA concerning Source Plasma (21 CFR Part 640 Subpart G), FDA memoranda, and BPC standard operating procedures. Bivigam is only manufactured from source plasma that is collected from healthy donors. The plasma is screened and with serological tests for HCV, HIV, and HBsAg, followed by minipool testing by NAT/PCR for HIV, HBV, HCV, HAV and Parvovirus B19. Plasma supplied to BPC is frozen, stored, and transported, under appropriately validated processes. Manufacturing plasma pools are tested for ----------(b)(4)---------- and Parvovirus DNA using NAT. The parvovirus B19 DNA limit for the manufacturing of plasma pools is set as $\leq 10^4$ IU/mL. All other raw materials used in the manufacture of Bivigam are obtained from appropriately qualified vendors, quarantined on receipt, tested by validated methods, and released to manufacturing by QA personnel. Biotest has committed to continuing process validation studies over a sufficiently large number of product lots in order to assure the robustness of the Bivigam manufacturing process.

Manufacturing process:

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BPC submitted this BLA in support of the manufacture of Immune Globulin Intravenous Human 10% (Bivigam®) at the Boca Raton, FL facility, and sterile filtration and filling of the final product at ----------(b)(4)----------.

The bulk drug substance is manufactured at the Biotest facility in Boca Raton, FL. -------
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A list of the products manufactured was provided and includes the following:

Product	Product Status	Final Product Stage
Bivigam	Developmental	BDS* and Intermediate
Nabi-HB (human hepatitis B immune globulin)	Commercial	BDS and Intermediate
----------(b)(4)----------	Commercial	Intermediate

* BDS = Bulk Drug Substance

Final drug product sterile filtration and fill is conducted at ----------
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Drug Product

Specifications: Specifications and validation of analytical methods have been evaluated by review personnel. The final specifications and acceptance limits established for Bivigam by BPC are within the ranges seen for other IGIV products (except for the product polysorbate 80, PS-80, levels discussed later) and were determined to be acceptable. These specifications are established based on the results of conformance batches, historical product data from BPC's other hyper-immune intravenous immunoglobulin products, and the outcome of clinical studies. The testing program for Bivigam includes appropriate measures of product quality attributes, product impurities, and parameters known to effect IGIV safety. All routine methods used as control or release testing of starting materials, process intermediates, drug product, and stability samples, were validated and appropriately implemented.

Comparabilty Testing of Conformance lots and Clinical Lots

The analytical characterization of the conformance lots manufactured after each phase of facility modifications performed by Biotest supported the comparability of Bivigam manufactured prior to and post-modifications to the facility. The comparability with the earlier clinical material was also supported by these studies. In additional Biotest performed similar comparability studies for their other licensed products made by the same manufacturing process and equipment.

Stability of IGIV Final Drug Product
The stability study data provided in the BLA was deemed sufficient to support the proposed storage conditions for final product Bivigam of 24 months at 2 °C to 8 °C. ----------(b)(4)----------.

Control of Adventitious Agents

The original BLA was submitted by Biotest Pharmaceuticals Corporation (BPC) on 03-NOV-2010 for the product of Immune Globulin Intravenous (Human), 10% Liquid (BIVIGAM). Viral safety data are included in the application to support the approval. The data were obtained from the following studies: 1) Plasma screening (serological testing for antibodies and antigen and NAT testing); 2) Analytical assay validation (Manufacturing pool testing); and 3) Manufacturing procedures that are validated for effectiveness of viral clearance.

Human Source Plasma (SP) for the production of BIVIGAM is obtained from FDA-licensed plasma collection centers in the United States. All plasma is tested by serological methods for anti-HIV and anti-HCV antibodies as well as HBsAg, and NAT tested for HAV, HBV, HCV, HIV and Parvovirus B19. The B19 DNA limit for the manufacturing plasma pools is set at less than or equal to 10^4 IU/mL.

Three manufacturing steps are designed specifically to contribute to the overall viral safety of the product: 1) precipitation and removal of Fraction III including Depth Filtration; 2) S/D treatment by TNBP/Triton X-100; and 3) 35 nm virus filtration. --(b)(4)-- treatment is embedded in both the S/D treatment step and the nanofiltration step. These manufacturing steps have been appropriately validated in scaled-down manufacturing. Robustness studies support that these steps are effective to remove/inactivate the viruses under worst-case conditions. The viral removal data are detailed in the table below.

Overall Log^{10} virus reduction factors by manufacturing steps of BIVIGAM

	Virus Removal/Inactivation (log^{10})								
Virus type Family	**Enveloped viruses**					**Non-enveloped viruses**			
	Retrovirus	**Flavivirus**			**Herpes**	**Picorna**	**Parvovirus**		**Polyoma**
Step/Virus	**HIV**	**BVDV**	**SinV**	**WNV**	**PRV**	**MEV**	**BPV**	**PPV**	**SV40**
Precipitation and Removal of Fraction III		**1.87**							**2.00**
Precipitation and Removal of Fraction III and Depth Filtration	--	**--**	--	--	--	**5.29**	--	**4.00**	--
TNBP/Triton X-100 Treatment	**> 4.43**	**> 5.04**	**> 7.11**	**> 4.96**	**> 4.01**	--	--	--	--
35 nm Virus Filtration	**> 5.19**	**> 4.88**	--	--	**> 4.64**	<1.0 *	**6.18**	< 1.0 *	**> 5.02**
Total Clearance	**> 9.62**	**> 11.79**	**> 7.11**	**> 4.96**	**> 8.65**	**5.29**	**6.18**	**4.00**	**> 7.02**

HIV:	Human immunodeficiency virus
BVDV:	Bovine viral diarrhea virus, model for HCV
SinV:	Sindbis virus, model for hepatitis C virus (HCV)
WNV:	West Nile Virus
PRV:	Pseudorabies virus, model virus for herpes viruses and hepatitis B virus
MEV:	Mink enteritis virus, model virus for hepatitis A virus
BPV:	Bovine parvovirus, model virus for human parvovirus B19
PPV:	Porcine parvovirus, model virus for human parvovirus B19
SV40:	Simian virus 40, model virus for highly resistant non enveloped viruses

CMC Conclusions

The CMC reviewers (M. Kennedy, M. Norton, D. Frazier, P. Zhang, L. Zhong) find that sufficient data and information have been provided on the chemistry, manufacturing, and controls to support licensure of Bivigam.

b) CBER Lot Release

Mode of Lot Release:
Confirmatory testing at CBER by Thrombin Generation Assay (TGA) is recommended for the IVIG final product. It is also recommended that CBER conduct HPLC testing of IgG monomer/dimer, IgG aggregates, and IgG fragments.

The product is an IGIV, similar to many other licensed IGIV products for which CBER does not perform routine lot release testing. The following lot release tests performed by BPC, in addition to the lot release testing performed by CBER (as noted above), are appropriate to assure the safety and potency of this product and include Sterility, Pyrogenicity, General Safety, ----------(b)(4)----------, Purity (Protein Composition, IgG), Identity, ----------(b)(4)----------. The results of these tests are reviewed upon submission of the Lot Release Protocol for each lot manufactured. The BLA submission review showed that all of the release tests are appropriately performed and validated.

The following forms the rationale for the testing plan:
Safety and Purity –

1. Tests for safety and purity performed by BPC and reviewed by CBER include: Sterility, Pyrogenicity, General Safety, ----------(b)(4)----------.
2. Bivigam is produced only from U.S. plasma collected at licensed U.S. blood collection centers. All plasma donations are screened for viral markers including anti-HIV 1 and 2 antibodies, HBsAg, and anti-HCV antibodies. Plasma is also tested by NAT for HIV, HAV, HBV, HCV and parvovirus B19. The parvovirus B19 DNA limit for the manufacturing plasma pools is set at less than or equal to 10^4 IU/mL.
3. BPC uses only U.S. sourced plasma in all of its manufacturing operations.
4. The manufacturing process for Bivigam contains no unusual or unique manufacturing steps, ----------(b)(4)----------.
5. The manufacturing process for Bivigam contains a number of robust viral clearance/ viral inactivation manufacturing steps.
6. Cold ethanol fractionation of human plasma is a widely used manufacturing process with a long history of producing high quality pharmaceutical products.
7. BPC has investigated the thrombotic activity of Bivigam and characterized the ability of the various manufacturing steps to remove thrombotic activity.

Potency and Identity –

1. Tests for potency and identity performed by BPC and reviewed by CBER include Purity (Protein Comp. IgG), Identity and ----------(b)(4)----------.
2. BPC has submitted in the BLA clinical trial results from well designed and appropriately executed clinical studies that support the efficacy of this product.

c) Facilities review/inspection

There is a single site for Drug Substance manufacturing:

> Biotest Pharmaceuticals Corporation; 5800 Park of Commerce Blvd NW, Boca Raton, Florida 33487

There is a single site for Drug Product filling and labeling:

> ----------(b)(4)----------

Under CBER SOPP 8410, DMPQ determined that a preapproval inspection of BPC was not needed since the facility was the subject of a Team Bio cGMP inspection in November 2010 that was designated Voluntary Action Indicated (VAI). The facility was undergoing modifications at the time of this inspection and was not operational so the impact of these facility modifications, which were part of the BLA submission, could not be assessed. The inability of the sponsor to complete these modifications in the expected timeline led to a delay in producing conformance lots needed for approval, which was a major element in the first CR Letter that was issued for this application. A second Team Bio inspection in May 2012 was focused on the facility modifications. This second inspection was classified as VAI. The product specialist on both inspections was the BLA chairperson Dr. Michael Kennedy.

DMPQ conducted a preapproval inspection (PAI) of the contract filler ----------
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d) Environmental Assessment

On December 19, 2012, DMPQ reviewer Destry Sillivan filed a memo recommending that BPC be granted a categorical exclusion under 21 CFR 25.31 (c) with the concurrence of the DMPQ Division Director.

4. Nonclinical Pharmacology/Toxicology

Based on the excipient profile of Bivigam®, the possibility exists for cardiovascular adverse events in human subjects (see discussion below). Hypersensitivity to glycine and PS80 containing products has been reported in the literature in both animals and humans. The potential also exists for renal or hepatic toxicity if Bivigam is used in susceptible populations, for example, patients with liver or renal impairment or very young and/or low birth weight infants.

From the nonclinical toxicology data, it is recommended that the BLA be approved for the proposed indication with a post marketing surveillance commitment that the patient population be monitored for cardiovascular, renal and hepatic toxicity.

Hypotension Related Temporally Associated Adverse Events (TEAEs)
Bivigam contains PS80 in higher concentration than other licensed IGIV products as noted in the table below.

Concentration of PS-80 in IGIV Products Product Name/Concentration (Sponsor)	**PS80 Concentration**
Gammaplex/(b)(4)(BPL)	--(b)(4)--
----------(b)(4)----------	--(b)(4)--
---------(b)(4)----------	--(b)(4)--
Hizentra/20% (CSL)	--(b)(4)--
Bivigam®/10% (Biotest)	--(b)(4)--

This issue was discussed with BPC at a pre-BLA meeting dated April 23, 2009 where FDA stated that PS80 has been reported to have a profound cardiovascular effect when given intravenously in a canine animal model, with a 60% drop in mean blood pressure and left ventricular maximum dP/dt for at least 30 minutes. BPC's response was that they would assess this cardiovascular effect based on safety data from their ongoing clinical trial. In their BLA submission, BPC has noted from animal studies that the effects of PS80 on myocardial contractility are "immediate, with onset occurring within minutes after administration. The effects disappear within 1 h after dosing is stopped." However, the cardiovascular effects may be species specific since these effects were not exhibited by non-human primates with the same exposure to PS-80.

BPC has estimated that the dose of PS-80 (0.25% = 2.5 mg/mL or 20 mg/mL) co-administered with the highest dose of Bivigam (800 mg/kg) is 1200 mg (assuming a 60 kg patient) and infusions with Bivigam are given over approximately 3.5 hours.

Taxotere® (docetaxel) is a chemotherapeutic agent licensed in the US for the treatment of breast cancer and other cancers. Taxotere contains PS-80 and results in higher human plasma concentrations than occur with Bivigam according to BPC's submission of data extracted from a report of Baker et al. [Simultaneous analysis of docetaxel and the formulation vehicle polysorbate 80 in human plasma by liquid chromatography/tandem mass spectrometry. **Anal. Biochem**. 2004; Jan 15,324(2):276-284]. Baker et al. reported the PS-80 plasma concentration over time with two doses of Taxotere. BPC used these plots to estimate concentration values of PS-80 at various time points after administration of Bivigam to human subjects. Their estimations showed that the total dose of PS-80 after administration of Taxotere was 1.5 to 4.7 times greater compared to the Bivigam formulation, the maximum plasma concentration of PS-80 after administration of Taxotere was 1.7 to 14.2 times greater compared to Bivigam and the area under the curve

value for the plasma-concentration profile for PS-80 administration of Taxotere was 1.0 to 6.0 times greater compared to Bivigam.

On April 22, 2011, BPC submitted the requested clinical information consisting of all subjects who experienced 1 or more drops in systolic blood pressure of 20 mmHg or more during any infusion of Bivigam as part of Amendment 0008 to the Bivigam BLA. Review of the data noted that 47 subjects out of 63 met this criterion. Some drops in blood pressure were isolated and others were sustained for more than one subsequent blood pressure reading. The data do not indicate that any decreases in blood pressure were clinically significant (they were asymptomatic) or were associated with any changes to the infusions. Fourteen of the 47 subjects experienced temporally associated adverse events (TAAEs) during the drops in blood pressure. However, none were related to the cardiovascular system.

Based upon the theoretical potential risk for severe hypotension from the animal data and the clinical data which showed that 75 percent of subjects had at least one drop in blood pressure $\geq$ 20 mmHg during an infusion of Bivigam, BPC has agreed to a post-marketing commitment to conduct a study to further evaluate the potential risk for hypotension during Bivigam infusion (see Section 11d "**Recommendation for Postmarketing Activities**"). The patients in this study will also be monitored for renal and hepatic toxicity.

It is recommended that the BLA be approved for the proposed indication with the above post marketing commitment.

5. Clinical Pharmacology

A pharmacokinetic study was conducted in 21 adult subjects. Five subjects were on a 3-week cycle and 16 subjects were on a 4-week cycle. The subjects received Bivigam 10% at a dose of 300-800 mg/kg administered by IV infusion over a maximum of 8 hours. PK parameters were assessed at infusion 13 for subjects on the 4-week infusion cycle or at Infusion 17 for subjects on the 3-week infusion cycle. Blood samples were collected prior to the start of each infusion and at 0.25, 1, and 24 hours and on days 3, 7, 14, 21, and 28. The pharmacokinetic parameters for total IgG are summarized below.

	3-week cycle (n = 5)	**4-week cycle (n = 16)**	**Total (n = 21)**
Statistic	**Mean (SD)**	**Mean (SD)**	**Mean (SD)**
Cmax (mg/dL)	2184 (293)	2122 (425)	2137 (392)
Cmin (mg/dL)	996 (176)	1106 (396)	1080 (355)

Tmax (hours)[a]	4.05 (2.67 – 26.1)	3.48 (2.58 – 78.6)	3.50 (2.58 – 78.6)
AUCtau (day*mg/dL)	27841 (4925)	35509 (6472)	33592 (6898)
t1/2 (days)	19.6 (4.14)	33.5 (10.7)	30.0 (11.2)
CL (dL/kg/day)	0.0197 (0.00223)	0.0141 (0.00463)	0.0155 (0.00480)
Vss (dL/kg)	0.584 (0.132)	0.640 (0.141)	0.626 (0.138)
MRT (day)	29.51 (5.18)	48.257 (14.6)	43.569 (15.2)

[a] Tmax = Time of maximum concentration; Median and range given due to extreme variability
AUCtau = area under the plasma concentration versus time curve with tau = end of the dosing interval; CL = clearance; Cmax = maximum concentration; Cmin = minimum concentration; n = number of subjects; SD = standard deviation; Tmax = time of maximum concentration; t1/2 = terminal half-life; Vss = volume of distribution; MRT = mean residence time

Conclusions
The clinical pharmacology reviewer (Harold Boxenbaum) considers this submission approvable on the basis of the pharmacokinetics information provided.

6. Clinical/ Statistical

a) Clinical Program
Nabi-7101 was conducted as a phase 3, multicenter, open-label clinical trial, with a total enrollment of 63 subjects, ages 6 – 75 years of age. Subjects had documented immune deficiency with agammaglobulinemia or hypogammaglobulinemia and were receiving IV immune globulin replacement therapy every 3 or 4 weeks. The objective of the trial was to evaluate the safety and efficacy of Bivigam, and to characterize its pharmacokinetic (PK) properties (see above).

During the trial, Bivigam was infused at a dose of 300-800 mg/kg per infusion at 3- or 4-week intervals, depending on the subject's previous IgG replacement schedule. Doses were adjusted in order to maintain serum trough total IgG concentrations > 500 mg/dL. Subjects received Bivigam for a total of 12 months and were followed-up for an additional 3 months (total of 15 months). The total duration of the trial was 22 months.

Efficacy was based upon the annual rate of acute serious bacterial infections (SBIs), defined as pneumonia, bacteremia/septicemia, osteomyelitis/septic arthritis, visceral abscess, and bacterial meningitis, per subject per year.

Based upon the observed rate of SBI of 0.035/person-years with an upper one-sided 99% confidence limit ≤0.136 in the intent-to-treat (ITT) population (N=58; data from 1 center [5 subjects] were excluded because of recurring protocol violations and deviations), BPC has provided adequate evidence for the efficacy of Bivigam by meeting the pre-specified, as per FDA guidance, primary efficacy endpoint of ≤1 SBI/subject/year with an upper one-sided 99% confidence limit less than 1. Further, data for secondary endpoints are supportive of Bivigam's efficacy.

The overall safety profile of Bivigam was acceptable as shown in the tabulated treatment-emergent adverse events (TEAEs) and temporally-associated adverse events (TAAEs), observed during the clinical trial. TAAEs are referred to as Adverse Reactions (ARs) in the Package Insert. No renal or hepatic adverse reactions were reported in the study. Study Nabi-7101 had a pre-specified, as per FDA guidance, target endpoint for safety of an upper one-sided 95% confidence limit of less than 0.40 when calculating the observed proportion of infusions with one or more TAAEs (an adverse event occurring within 72 hours during or after an infusion of Bivigam). BPC met this pre-specified safety endpoint with an upper one-sided confidence limit of less than 0.36.

Study Nabi-7101 began with the dosing schedule of 300 to 600 mg/kg. This dosing schedule was increased to 300 to 800 mg/kg in Amendment 1 to the protocol dated 17 Jul 2007 (original protocol dated 29 Mar 2007) "at the recommendation of several of the study's investigators at the Investigator Meeting on 13-14 July 2007". Thirteen of the 63 subjects in the Safety Population, approximately 20%, received doses in excess of 600 mg/kg. The safety profile at the higher doses (>600 mg/kg) was acceptable and the number of subjects who received higher doses was acceptable to support labeling up to 800 mg/kg.

Bivigam contains polysorbate 80 (PS-80) in higher concentration (approximately 10 fold), as compared to other licensed IGIV products. PS-80 is used as a stabilizer in Bivigam. PS-80 has been reported to have a negative inotropic effect when given IV in a canine animal model, with a resultant 60% decrease in mean arterial pressure and left ventricular maximum contractility. The effect lasts approximately 30 minutes. The exposure to PS-80 in the canine model was similar to the exposure in a patient administered the highest dose of Bivigam (approximately 20 mg/kg of PS-80). However, the cardiovascular effects may be species specific since these effects were not exhibited by non-human primates with the same exposure to PS-80.

In Study Nabi-7101, 47 of the 63 subjects in the Safety Population had at least one episode of a drop in systolic blood pressure greater than 20 mmHg during an infusion. None of these events were symptomatic or led to a clinically relevant outcome (change in the rate of infusion; or stopping of infusion). Hypotension has been reported at a rate ≤ 20

percent in clinical trials with some IGIV products. In order to further assess this potential risk BPC agreed to conduct a post-marketing observational safety study by August 2016.

It is recommended that Bivigam be approved for the proposed indication and that the potential risk of hypotension due to a higher concentration of PS-80 be addressed via a post-marketing study commitment. The patients in this study will also be monitored for renal and hepatic toxicity because of the potential for renal or hepatic toxicity in susceptible populations, as noted in Section 4 "Nonclinical Pharmacology/Toxicology".

In designing the protocol for this study, the following guidelines were followed:

- US Food and Drug Administration: *Safety, Efficacy and Pharmacokinetic Studies to Support Marketing of Immune Globulin Intravenous (Human) as Replacement Therapy for Primary Humoral Immunodeficiency*
- Committee for Proprietary Medicinal Products: *Note for Guidance on the Clinical Investigation of Human Normal Immunoglobulin for Intravenous Administration (IGIV)*

Statistical Analysis

The sponsor has submitted the results of a single, open-arm, phase 3 trial with 63 subjects to support the efficacy of the proposed product, Immune Globulin Intravenous Human 10% (Bivigam) for the treatment of Primary Immune Deficiency Disorders (PIDD).

This study was an open-label, phase 3, multi-center (15 centers), safety, efficacy, and pharmacokinetic study (Nabi-7101) of Nabi-IGIV 10% Immune globulin intravenous (human; proposed trade name: Bivigam) in subjects with primary immune deficiency disorders (PIDD). The primary efficacy endpoint is the rate of Serious Bacterial Infections (SBIs) occurring after the first infusion of Bivigam and before or on the date of the final clinical visit, per person-year. The rate of SBI is defined as total number of SBIs divided by the total person-year for the following types of infections: bacteremia/sepsis, bacterial meningitis, osteomyelitis/septic arthritis, bacterial pneumonia, and visceral abscess. The primary safety endpoint is the proportion of infusions with one or more infusion–related (TAAE: temporally associated with an infusion, i.e., within 72 hours of the infusion) adverse events (AEs).

Study design: This was an open-label study in 15 centers. Biotest-IGIV 10% was administered at 300 to 800 mg/kg at 3- or 4- week intervals depending on the previous schedule for approximately 12 months. Subjects were followed-up for an additional 3 months (total of 15 months).

Study subjects: There were 63 subjects in the safety, 58 subjects in the Intent-to-Treat (ITT), and 51 in the Per-Protocol (PP) population with 32 women and 31 men with a mean age of 41 years. There were 44 subjects between 18 and 64 years of age (69.8%), 4 children (6.3%) between 6 and 11 years of age, 6 adolescents (9.5%) between 12 and 17 years of age, and 9 elderly subjects (≥65 years of age).

There were two SBIs (two subjects with bacterial pneumonia) during the study for a rate of SBI per person-years of 0.035 (2 of 58) for intent-to-treat (ITT) and 0.04 (2 of 51) for per-protocol (PP) population. There were no deaths during the study. The proportion of infusions with one or more infusion related adverse events in this study was lower than the pre-specified endpoint. These open label study safety data supported the safety of the proposed product for its stated indication.

Statistical Conclusions:

The infusion of Bivigam 10% met the primary efficacy and safety objectives of the study and met the pre-specified endpoints by demonstration of one sided upper 99% upper confidence limit for the rate of SBIs per person-year is less than 1 for efficacy and one-sided 95% upper confidence limit for the proportion of infusions with one or more temporally associated AEs is less than 40%. The statistical reviewer has no objection to the licensure of this product.

b) Pediatrics

The Pediatrics Review Committee waived and deferred the following Pediatric Research Equity Act (PREA) requirements, under 21 U.S.C. 355c for the conduct of pediatric studies:

- The pediatric study requirement for ages [0] to [<2] years was waived because the necessary studies are impossible or highly impracticable. It is rare for primary humoral immunodeficiency to be diagnosed in this age group.

- The submission of BPC's pediatric study for ages [≥2] to [16] years was deferred for this application because this product is ready for approval for use in adults and the pediatric study has not been initiated. Please see the post-marketing requirement that was put in place for this pediatric study in section 11 (d), below.

c) Other Special Populations
No other special populations are under consideration for the use of this IGIV product.

d) Overall Comparability Assessment
The review committee has determined that Bivigam has comparable product efficacy, safety profile, manufacturing quality, product stability, product specifications, and product purity, to other IGIV's currently being marketed for the treatment of PIDD.

Bioresearch Monitoring (BIMO) summary of Clinical Site Inspections

The results of Bioresearch Monitoring inspections of four clinical sites did not reveal problems that impact the data submitted in the application. There were four (4) clinical investigator inspections performed in support of the Biologics License Application (BLA) supplement conducted in accordance with FDA's Compliance Program Guidance Manual (CPGM) 7348.811, Inspection Program for Clinical Investigators. The inspections represented approximately 39% of the total subjects enrolled in **NABI-7101.**

The inspection assignment included specific questions in reference to the study protocol and verification of the study data on safety and efficacy endpoints submitted by the sponsor in the BLA supplement.

NOTEWORTHY INSPECTIONAL FINDINGS

1. Failure to ensure that the investigation was conducted according to the investigational plan.

    - Protocol Inclusion Criteria states the subject must currently be on an IGIV replacement therapy at a fixed interval and dosage between 300 and 800 mg/kg. Site 014 enrolled subject # (b)(6) who did not meet eligibility dosing requirements at screening. The same subject received a total IGIV infusion of 275 mg/kg throughout the study. The study protocol states each subject will receive a total IGIV infusion of 300 – 800 mg/kg per month.

    - The protocol states the initial infusion rate will be 30mL/kg/hr (30mg/kg/hr) for 10 minutes and if well tolerated, the rate can be increased to 50 mg/kg/hr at 20 minutes. Site 014 increased infusion rates prior to the 10 minutes (initial rate) or 20 minutes (subsequent rate increases) for 3 of the 5 subjects enrolled at the site.

    - The Protocol states all subjects are required to give their informed consent prior to the performance of any clinical activities or procedures. The informed consent form for Site 007 had 3 versions during the study, and 5 of the 7 subjects enrolled in the study did not sign the most current Institutional Review Board (IRB) approved consent forms at their next visits for study drug infusions and/ or study related testing.

For the four clinical sites inspected, there was no evidence of under-reporting of adverse events and no discrepancies noted between the source documents, Case Report Forms's and the data submitted in the BLA.

7. Safety

The overall safety profile of Bivigam was acceptable as shown in the tabulated treatment-emergent adverse events (TEAEs) and temporally-associated adverse events (TAAEs), referred to as Adverse Reactions (ARs) in the Package Insert, observed during the clinical trial. Study Nabi-7101 had a pre-specified target endpoint for safety of an upper one-sided 95% confidence limit of less than 0.40 when calculating the observed proportion of infusions with one or more TAAEs (an adverse event occurring within 72 hours during or after an infusion of Bivigam). BPC met this pre-specified safety endpoint with an upper one-sided confidence limit of less than 0.36.

8. Advisory Committee Meeting

There were no issues related to this product that prompted the need for discussion by the Blood Products Advisory Committee.

9. Other Relevant Regulatory Issues

There were no other regulatory issues raised during the review of this BLA.

10. Labeling

Proprietary Name: The sponsor's proprietary name, BIVIGAM, was reviewed by the Advertising and Promotional Labeling Branch (APLB) and was found to be acceptable upon initial review.

Physician labeling: The final Bivigam labeling is Physicians Labeling Rule compliant.

Full Prescribing Information (FPI): APLB reviewed the original FPI submitted by the applicant. Comments from a promotional and comprehension perspective were provided to OBRR on Jun 30, 2011.

Comments regarding the FPI were conveyed to the applicant on July 17, 2011. The applicant subsequently submitted a revised FPI in October, 2011. APLB reviewed the revised FPI on December 10, 2011 and provided additional comments to OBBR for discussion with the applicant. FDA's comments were conveyed to the applicant on December 17, 2011. Additional comments were submitted to the applicant on April 2, 2012. The applicant accepted all of FDA's remaining comments and recommendations. All FPI issues have been adequately resolved in preparation of final approved labeling.

Carton and immediate container labels: The carton and container labeling submitted in the original application was reviewed by APLB. Initial comments from a promotional and comprehension perspective were provided on December 10, 2010. The applicant was informed on December 17 of initial carton issues (non-compliance with 21 CFR 610.62). The sponsor submitted revised carton and container labeling on February 8, 2012, in response to which APLB provided additional comments to the applicant. A third revision of the carton and labels was submitted on March 2, 2012. It was reviewed and found to be acceptable by APLB and OBRR. All carton/container labeling issues were adequately resolved.

11. Recommendations and Risk/ Benefit Assessment

a) Recommended Regulatory Action

This BLA is recommended for approval with a number of Post-Marketing Commitments.

b) Risk/ Benefit Assessment

Data submitted to the BLA establish a substantial likelihood of benefit in the target population of adults with PIDD. The only potential additional risks with the use of the

product over other IGIV products currently licensed are the theoretical potential for clinically significant hypotension during infusion related to increased levels of PS-80 and for renal or hepatic toxicity in susceptible populations; therefore, the overall benefit-risk profile is favorable.

The clinical data showed 75 percent of subjects during the clinical trial had at least one decrease in blood pressure ≥ 20 mmHg during an infusion. No subject during the study experienced an adverse event related to renal or hepatic toxicity. Therefore, these theoretical risks will be evaluated by a post-marketing commitment and the overall benefit-risk profile is favorable for licensure.

c) Recommendation for Postmarketing Risk Management Activities

A pharmacovigilance plan has been developed by BPC, and has been reviewed and was found to be acceptable. BPC has proposed to address pharmacovigilance of Bivigam through the collection of adverse events (AE) from "all sources" and assessment of the data through BPC's Corporate Drug Safety department. BPC intends to summarize and report known IGIV class effects in periodic safety update reports (PSURs). With regard to the risk of hypotension due to PS-80, BPC intends to "specifically discuss and address any spontaneous AEs reported for hypotension in PSURs".

OBE and OBRR agree with the plan for routine pharmacovigilance as proposed by BPC.

d) Recommendation for Postmarketing Activities:

PEDIATRIC REQUIREMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication in pediatric patients unless this requirement is waived, deferred, or inapplicable.

We are waiving the pediatric study requirement for ages 0 to < 2 years because:

1. Necessary studies are impossible or highly impracticable. This is because of the rarity of diagnosis in this age group.

We are deferring submission of your pediatric study(ies) for ages 2 to 16 years for this application because:

1. This product is ready for approval for use in adults and the pediatric study(ies) has/have not been completed.

The deferred pediatric study(ies) required under 505B(a) of the Federal Food, Drug, and Cosmetic Act is/are required postmarketing study(ies). The status of this/these postmarketing study(ies) must be reported according to 21 CFR 601.70 and section 505B(a)(3)(B) of the Federal Food, Drug, and Cosmetic Act. This/these required study(ies) is/are listed below:

1. A Phase IV, Multicentre, Open-Label Study to Evaluate the Efficacy and Safety of BIVIGAM™ in Primary Immune Deficiency Disorders in Children and Adolescents ages 2 to 16.

Final Protocol Submission Date: July 2013

Study Completion Date: July 2017

Final Report Submission Date: October 2017

Submit final study reports to this BLA. For administrative purposes, all submissions related to this/these required pediatric postmarketing study(ies) must be clearly designated **"Required Pediatric Assessment(s)."**

AGREED UPON POSTMARKETING COMMITMENTS

The sponsor has committed to the following:

Postmarketing Studies subject to reporting requirements of 21 CFR 601.70.

1. Prospective, non-interventional, active-control, observational safety study to further assess the potential risk of hypotension, hepatic and renal impairment in Bivigam-treated patients with primary humoral immunodeficiency (PI).

Final Protocol Submission Date: July 2013

Study Completion Date: September 2017

Final Report Submission Date: December 2017

The following CMC related Post-Marketing Commitments were agreed to by BPC:

1. ----------(b)(4)----------.

1 page redacted (b)(4)